Fang et al., Afr J Tradit Complement Altern Med., (2017) 14 (4): 297-319
https://doi.org/10.21010/ajtcam.v14i4.33

CHINESE HERBAL DECOCTION AS A COMPLEMENTARY THERAPY FOR ATROPHIC GASTRITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Chinese herbal decoction (CHD) has been extensively used in the treatment of atrophic gastritis (AG) in China and other Far Eastern countries. We conducted a systematic review and meta-analysis to estimate the efficacy and safety of CHD in AG.
Materials and Methods: Pubmed, Embase, Cochrane central register of controlled trials (central), VIP, China National Knowledge Infrastructure, Sinomed, Wanfang data were searched (up to December 2015). Randomized controlled trials recruiting patients with AG comparing CHD (alone or with western medicine (WM)) with WM were eligible. Dichotomous data were pooled to obtain relative risk (RR), with a 95% confidence interval (CI).
Results: Forty-two articles including 3,874 patients were identified. CHD, used alone or with WM, had beneficial effect over WM in the improvement of clinical manifestations (RR=1.28; 95% CI 1.22-1.34) and pathological change (RR=1.42; 95% CI 1.30-1.54) for AG patients. However, the *H. pylori* eradication effect of CHD was not supported by the existing clinical evidence, because of the significant study heterogeneity (I^2>50%) and inconsistency between the primary results and sensitivity analysis.
Conclusions: CHD, if prescribed as a complementary therapy to WM, may improve the clinical manifestations and pathological change for AG patients. But its monotherapy for *H. pylori* eradication is not supported by enough clinical evidence.

Key words: atrophic gastritis; *Helicobacter pylori*; Chinese herbal decoction; meta-analysis

Abbreviations: AG, atrophic gastritis; **TCM**, traditional Chinese medicine; **CHD**, Chinese herbal decoction; **WM**, western medicine; **Int. CHD-WM**, integration of Chinese herbal decoction and western medicine; **RCTs**, randomized controlled trials; **RR**, relative risk; **CI**, confidence interval; **I^2**, inconsistency index

Introduction

Atrophic gastritis (AG) is defined as the non-metaplastic and metaplastic atrophy of gastric mucosa which is replaced by connective tissue or glandular structures inappropriate for location, such as intestinal-type epithelium and pyloric-type glands (Rugge et al., 2011). Epidemiological surveys revealed that the global incidence of AG is about 0-10.9% (Adamu et al., 2010), and the prevalences are higher in Far Eastern countries (such as China, Japan, and Korea) than those in the western ones (Aoki et al., 2005; Weck and Brenner,2006; Weck et al., 2007). The persistent *H. pylori*-related inflammatory condition is one of the most important pathogeneses of AG (Eid and Moss, 2002), making the risk for intestinal-type gastric cancer 5.13 to 24.71-fold higher in gastritis patients than in normal people (Kato et al., 1992). *H. pylori* eradication therapies, such as the one-week combined use of moxifloxacin, tetracycline and lansoprazole, are recommended by the western medicine (WM) system to control AG (Taş et al., 2011). However, some recent studies reported that the clinical eradication rate of *H. pylori* has decreased to an unacceptable low level of 25%-80% (Gisbert et al., 2007; Graham and Fischbach,2010; Gumurdulu et al., 2004). The main causes of eradication failure are the poor compliance of patients, emerging resistant *H. pylori* strains and adverse drug reactions (Graham and Fischbach, 2010; Megraud, 2004; Safavi et al., 2015). The unsatisfactory efficacy and safety in WM emphasize the need for more alternative approaches to the managing AG.

Traditional Chinese Medicine (TCM) has been widely used for treating gastritis in China and other Far Eastern

countries for tens of centuries (Chen et al., 2003; Qin et al., 2013; Tang et al., 2016; Xia,2004). Nowadays, Chinese physicians often prescribe TCM combined with WM, in the belief that patients will benefit from both the western and Chinese traditional therapies (Lu and Chen, 2015). Among the widely-used herbal decoctions, tens of herbs (e.g. *Abrus cantoniensis* Hance, *Saussurea lappa* (Decne.) Sch.Bip, *Eugenia caryophyllata* Thunb) showed potent anti-*H. pylori* activity (MICs: ~40μg/ml) (Li et al., 2005; Safavi et al., 2015). Certain herbal extracts were also proved to effectively exhibit anti-inflammatory activity and reduce gastric symptoms by suppressing the production of nitric oxide, prostaglandin E(2), cyclooxygenase-2, TNF-α, IL-6 and interleukin 1β (Meng and Yang, 2010; Song et al., 2009). Clinical trials showed that some Chinese decoctions or herbal extracts were effective in alleviating AG symptoms and eradicating *H. pylori* (Meng and Yang,2010; Song et al., 2009), without increasing the incidence of adverse effects or producing resistant colonies (Higuchi et al., 1999). Although TCM may be a promising supplement to WM, there is no evidence from large-scale, multicenter clinical trials on its clinical use. Hence, we performed a systematic review and meta-analysis to evaluate the efficacy and safety of Chinese herbal decoction (CHD), the most essential and traditional part of TCM, for AG treatment.

Material and methods

Search strategy and study selection

A comprehensive retrieval was conducted in seven electronic databases of PubMed (1966 to December 2015), Embase (1980 to December 2015), Cochrane central register of controlled trials (central) (Issue 7, 2015), Sinomed (up to 2015), VIP Information (up to 2015), China National Knowledge Infrastructure (up to 2015) and Wangfang Data (up to 2015), without language restriction. AG of *H. pylori* origin, rather than autoimmune origin, was included in this study. Only randomized controlled trials (RCTs) were eligible for inclusion in this review. Trials should compare CHD (used alone or plus WM) versus WM. In WM group, patients with gastrointestinal symptoms (gastrectasia, stomach-ache, dyspepsia, *etc*.) should be alleviated by medications such as proton pump inhibitor; and patients with *H. pylori* should be treated with eradication therapy, such as triple therapy. AG should be diagnosed according to case history and pathological diagnosis (atrophy of the gastric mucosa, intestinal metaplasia, atypical hyperplasia, inflammatory cell infiltration, exposed sub-mucosal vessels). Diagnosis of *H. pylori* should be based invasively on endoscopic biopsy check with a rapid urease test, histological examination, or microbial culture; or noninvasively on a blood antibody test, stool antigen test, or carbon urea breath test. Efficacy is assessed by improvement of clinical manifestations (alleviation of gastrectasia, stomach-ache, dyspepsia, *etc*.), pathological diagnosis (alleviation of atrophy of the gastric mucosa, intestinal metaplasia, atypical hyperplasia, inflammatory cell infiltration, and exposed submucosal vessels), and the eradication of *H. pylori*. The authors of related studies were contacted to provide additional information on trials where required. Search terms used in this study were *traditional Chinese medicine, herbal medicine, atrophic gastritis, randomized controlled trial, phytotherapy* (both as medical subject heading (MeSH) and free text terms), or the following free text terms: *herbal, Chinese medicine, traditional medicine,* and the names of widely used formulae, such as *Ban-Xia-Xie-Xin* decoction, *Wei-Su-Chong-Ji* decoction, *Xiao-Jian-Zhong* decoction, *Hou-Bu-Wen-Zhong* decoction, *etc*. We also searched the reference lists of the original reports, reviews, and letters to the editor, case reports and meta-analyses of studies to identify studies which had not yet been included in the computerized databases. The last search was performed on 1st December 2015. Two reviewers (WJF, XYZ) independently assessed the eligibility of each study to be included in our meta-analysis using predesigned eligibility forms according to eligible criteria, and this was checked by another author (BY). Any disagreement was resolved by consensus between the two reviewers (SJS, ZM), adjudicated with the support of a third reviewer (BY).

Data collection process and data items

Data extraction were performed by three reviewers (WJF, XYZ, BY) with a Microsoft Excel spreadsheet (XP professional edition; Microsoft, Redmond, Washington, USA), and any disagreement was resolved by discussion. We consulted authors of the original studies through emails to get information if any problem occurred. The following data were collected: study design, sample size, therapeutic duration, criteria for efficacy judgment, intervention and control, eradication rate of *H. pylori*, clinical manifestation improvement, pathological improvement, adverse events.

Assessment of risk of bias

The studies were appraised independently by two authors (WJF, XYZ). Considering the different features of CHD from WM, we appropriately modified the Jadad scale, as some previous meta-analyses did. (Xu. et al.,2011; Zou et al,. 2011) The modified Jadad scale was as follows: (1) was the study described as randomized? (2-properly with detailed description of randomization, 1-randomized but detail not reported, 0-inappropriate randomization); (2) was allocation concealment used? (2-properly used, 1-unclear, 0-not used); (3) was the blind method used? (2-double-blind, 1-single-blind, 0-open-label); (4) were dropout and follow-up reported? (1-numbers and reasons reported, 0-not

reported); and (5) was the treatment based on TCM symptom types (also called *Bianzheng Lunzhi* in Chinese (Karchmer,2013))? (2-properly with detailed description, 1-mentioned but detail not reported, 0-not mentioned or inappropriate). A study with a quality score ≤2 was considered as a study at high risk of bias, a study with a quality score ≥ 5 was considered as a study at low risk of bias, and the left were at moderate risk of bias.

Summary measures and synthesis of results

We undertook separate synthesis for each comparison. Dichotomous data were summarized as relative risk (RR) with 95% Confident Intervals (CIs), and a random effects model (DerSimonian and Laird,1986) was used whether heterogeneity was found in order to gain a more conservative outcome. When the authors reported dichotomous data (effective or ineffective), we retrieved them directly. In studies where multiple strata were given to define improvement, we converted these outcomes into dichotomous data to permit the overall analysis. Since the included study use the same validated criteria for the judgement of cure, we grouped together *cure*, *significant improvement*, and *improvement* as effective and *no improvement*, *deterioration*, as ineffective. Publication bias was examined using funnel plot and Egger's tests. Heterogeneity between studies was tested using the inconsistency index (I^2) statistic with a cutoff of 50%. The statistical analysis was carried out with RevMan 5.0 software (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Stata/SE version 10.0 (StataCorp, College Station, Texas, USA).

Sensitivity analysis

Because the poor-quality of RCT design might lead to exaggerated estimates of intervention benefit (Kjaergard et al.,2001), sensitivity analyses were performed to evaluate the robustness of outcomes and identify sources of heterogeneity. We conducted predesigned sensitivity analyses among studies of low to moderate risk of bias (modified Jadad score ≤2).

Results

Study characteristics and risk of bias

The search strategy was shown in the flow diagram (Figure 1). We included 42 RCTs, involving 21 studies (n=2,024) comparing CHD monotherapy with WM and 21 studies (n=1,850) comparing integration of CHD and WM (Int. CHD-WM with WM). According to the modified Jadad scale, totally 25 RCTs are at moderate risk of bias, 18 are at high risk of bias (see Supplementary Table 1). Study design details of each RCTs were shown in Supplementary Table 2, and the relationship among Chinese *PinYin* names, Chinese names, English names and Latin names of herbs mentioned in Supplementary Table 2 were demonstrated in Supplementary Table 3.

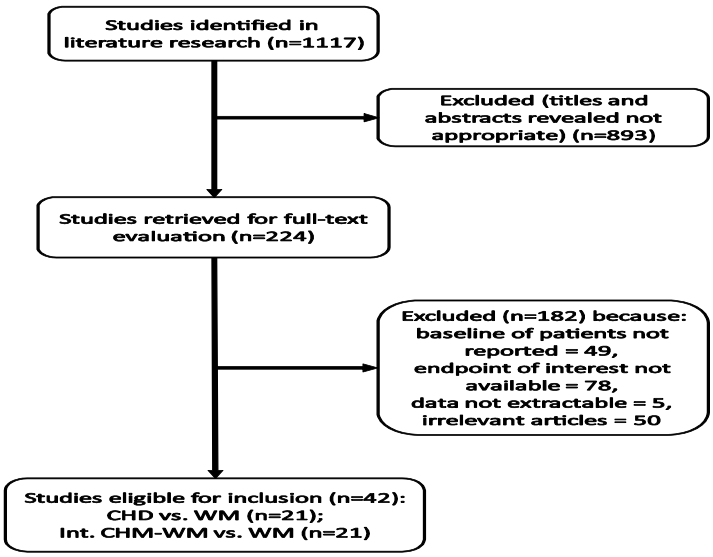

Figure 1: Flow diagram of RCTs included (Note: RCT, randomized controlled trial)

https://doi.org/10.21010/ajtcam.v14i4.33

Supplementary Table 1: Modified Jadad score of the included RCTs

1. CHD vs. WM

Trial	*Year*	*Randomized*	*Allocation concealment*	*Blind*	*Dropout*	*Treatment based on TCM syndromes*	*Modified Jadad score*
Wei BQ	2003	1	0	0	0	2	3
Gong DH	2004	1	0	0	0	2	3
Li JR	2005	1	0	0	0	2	3
Wang HY	2005	1	0	0	0	1	2
Wei YQ	2005	1	0	0	0	2	3
Kan SY	2006	1	0	0	0	2	3
Meng ZJ	2006	1	0	0	0	2	3
Zhao HB	2006	1	0	0	0	0	1
Chen YJ	2007	1	0	0	0	1	2
Luo LB	2007	1	0	0	0	2	3
Zhao M	2007	1	0	0	0	2	3
Ou WE	2008	1	0	0	0	2	3
Wang ZM	2008	1	0	0	0	2	3
Xiao LD	2008	1	0	0	0	0	1
Shi CH	2009	1	0	0	0	2	3
Shu H	2009	1	0	0	0	2	3
Su XH	2009	2	0	0	0	2	4
Li LH	2010	1	0	0	0	0	1
Meng L	2010	1	0	0	0	1	2
Zhang YM	2011	1	0	0	0	2	3
Zhu XP	2013	1	0	0	0	2	3

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2. Int. CHD-WM vs. WM

Trial	*Year*	*Randomized*	*Allocation concealment*	*Blind*	*Dropout*	*Treatment based on TCM syndromes*	*Modified Jadad score*
Wang HB	2003	1	0	0	0	0	1
Yue WJ	2003	1	0	0	0	2	3
Zhou AX	2006	1	0	0	0	2	3
Shen Y	2007	1	0	0	0	0	1
Xiang SY	2007	1	0	0	0	0	1
Zhang DF	2008	1	0	0	0	0	1
Gao Z	2009	1	0		0	0	1
Huang GC	2009	1	0	0	0	1	2
Lei CH	2009	1	0	0	1	2	4
Ma J	2009	1	0	0	0	2	3
Song FL	2009	1	0	0	0	2	3
Liu HR	2010	2	0	0	0	0	2
Kuang YJ	2011	1	0	0	0	2	3
Wang XF	2011	1	0	0	0	2	1
Li SQ	2012	1	0	0	0	2	3
Zhang WH	2012	1	0	0	0	0	1
Han XF	2013	1	0	0	0	2	3
Wang J	2013	1	0	0	0	2	1
Shan Q	2014	1	0	0	0	2	3
Fu HK	2014	1	0	0	0	2	3
Liu DX	2014	1	0	0	0	0	1

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Supplementary Table 2: Study design details of the included RCTs
1: CHD vs. WM

Author	DOI/ Website	Duration of clinical trail	Year of publication	Age [range]	Participants (male/female)	Number of Intervention/ Control	Intervention	Control	Duration of therapy	Adverse events
Zhu XP	10.3969/j.issn.1003-5699.2007.03.015	2003-2013	2013	[23, 67]	60 (43/17)	30/30	Chai-Hu-Shu-Gan Decoction [ChaiHu 20g, DanShen 20g, FuLing 20g, NanShaShen 15g, BaiZhu 14g, TaiYangHua 14g, ZeXie 14g, BaiShao 12g, ChiShao12g, RouDoukou 12g, TanXiang 6g, HuangLian 6g, BanXia 6g, ZhiGanCao 6g]	Domperidone, Bismuth Biskalcitrate, Triple therapy	28 days	Not reported
Zhang YM	10.3969/j.issn.1006-0979.2011.08.004	2000-2010	2011	[28, 69]	120 (63/57)	60/60	Tianqi 5g, BanXie 6g, GanCao 10g, HuangQin 10g, ZhiKe 10g, BaiShao 12g, PuGongYing 15g, DangGui 15g, NanShaShen 15g, MaiDong 15g, BaiZhu 15g, DangShen 15g, DanShen 30g, HuangQi 45g	Colloidal Bismuth Pectin, Metronidazole, Domperidone, Amoxicillin	60 days	Not reported
Li LH	http://www.cnki.com.cn/Article/CJFDTOTAL-SCZY201011038.htm	2006-2009	2010	[33, 72]	55 (30/25)	30/25	HuangQi 30g, TaiZiShen 30g, BaiZhu 20g, ShanYao 30g, NanShaShen 15g, YuZhu 15g, BaiHe 15g, MaiDong 20g, NvZhenZi 20g, LiChang 20g, DanShen 30g, PuHuang 15g, GanCao 10g.	Vitacoenzyme Tablets, Colloidal Bismuth Pectin, Compound Pepsin	3 months	Not reported
Meng L	http://www.cnki.com.cn/Article/CJFDTotal-LZXB201004078.htm	2004-2008	2010	[41, 72]	84 (57/27)	56/28	Shan-Jia-Yu-Wei Decoction [PaoShanJia 6g, ZaoCi 10g, TongHuaGen 10g, ChaiHu 10g, FoShou 15g, ZhiKe 15g, TaoRen 10g, HongHua 10g, JiNeiJin 30g, JiaoSanXian 30g, HuangLian l0g, WuZhuYu 3g, PuGongYing 10g, FuLing 30g, BaiZhu 30g, BaiJi 30g, BaiShao 15g, GanCao 6g]	Vitacoenzyme Tablets, Domperidone	60 days	Not reported
Shi CH	10.3969/j.issn.1671-038X.2009.06.018	2006-2009	2009	[17, 62]	76	46/30	Jian-Pi-Yi-Wei Decoction [TaiZiShen 25g, BaiZhu 10g, MuXiang 10g, ShaRen 10g, BeiMu10g, PuHuang 15g, LianQiao 12g, MoYuGu 15g, MaiDong 10g, NanShaShen 20g]	Vitacoenzyme Tablets or Gefarnate. Patients with H.pylori infection: Tinidazole, Amoxicillin, Omeprazole, patients with bile regurgitation: Talcid, patients with gastrectasia: Domperidone	90 days	Not reported
Su XH	http://d.g.wanfangdata.com.cn/Periodical	2000-2008	2009	No data	120 (60/60)	62/58	Gan-Cao-Xie-Xin Decoction [GanCao 10g, BanXie 12g, HuangQi 15g, HuangLian 10g, DangShen 30g, HuangQi 30g, ShanYao 15g, ChaiHu 15g]	Amoxicillin, Clarithromycin, Domperidone	3 months	Not reported

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Shu H	10.3969/j.issn .1005-7072.2 009.02.028	2004-2007	2009	[24, 65]	58 (23/35)	30/28	Shen-Shi-Yang-Wei Decoction [DangShen 20g, HuangQi 30g, BaiZhu 15g, DanShen 30g, DangGui20g, ChiShao 15g, GanCao 6g]	Domperidone, Vitacoenzyme Tablets. Patients with H. pylori: De Nol, Amoxicillin	intervention: 69days, control: less than 4 weeks	Not reported
Wang ZM	10.3969/j.issn .1009-5519.2 008.12.111	2005-2007	2008	[34, 65]	78 (46/32)	45/33	BanXie 12g, HuangLian 6g, HuangQi 12g, GanJiang 12g, TaiZiShen 20g, GanCao 9g, ChaiHu 12g, ZhiKe 15g, XiangFu 10g, ChuanXiong 12g, BaiShao 18g, MuXiang 12g, ShaRen 10g, FoShou 12g, FoShou 12g	Hydrotalcite tablet, Mosapride	3 months	Not reported
Ou WE	10.3969/j.issn .1003-7705.2 008.02.015	1994-2008	2008	No data	172 (106/66)	86/86	YanHuSuo 15g, DanShen 15g, ShanZha 15g, Tianqi 3g, PuHuang 10g, DangGui 20g, BaiJi 20g, RuXiang 10g, WuYao 10g, BaiHe 30g, BaiShao 15g, ShiHu 15g, NanShaShen 15g, GanCao 5g	Vitacoenzyme Tablets, Domperidone	3 months	one case reported urticaria in intervention
Xiao LD	10.3969/j.issn .1673-7717.2 008.05.051	2006-2007	2008	[19, 77]	60 (36/ 24)	30/30	Wei-Yan Decoction [PuGongYing 30g, BaiHuaSheSheCao 30g, HuangLian 6g, HuangQi 10g, DanShen 20g, HuangQi 15g, BaiZhu 15g, FuLing 15g, BanXie 10g, ChenPi 10g, WaLengZi 30g, MoYuGu 30g, JiangHuang 15g, GanJiang 8g]	Omeprazole, Clarithromycin, Amoxicillin	intervention: 20 days, control: 7 days	Not reported
Chen YJ	10.3969/j.issn .1006-6233.2 007.03.030	2000-2006	2007	[23, 70]	92 (49/43)	50/42	Jian-Pi-Yang-Ying-He-Wei Decoction [TaiZiShen, WuZhiMaoTao, ShiHu, FoShou, YanHuSuo, NanShaShen, BaiJi, DanShen, MaiDong]	Marzulene S	24 weeks	Not reported
Luo LB	10.3969/j.issn .1000-7369.2 007.09.032	2002-2006	2007	[25, 73]	82 (55/27)	42/40	Man-Wei-Ning Decoction [DangShen 15g, WuZao 15g, ZhiKe 10g, DangGui 10g, BaoShao 20g, HuangQi 20g, YanHuSuo 12g, GanCao 6g, TianQi 4g]	Bismuth Potassium Citrate Capsules	8 weeks	six cases reported nausea, vomit or constipatio n in control
Zhao M	10.3969/j.issn .1000-7369.2 007.09.029	2007	2007	[31, 50]	64	32/32	(1) For TCM syndrome of Weakness of Spleen and Stomach: HuangQi 15g, DangShen 15g, BaiZhu 10g, FuLing 10g, BaiShao 10g, GanCao 10g, ShengJiang 10g, DaZao 6g, ShaRen 6g, (2) for TCM syndrome of Coke and Blood Stasis: BanXie 10g, ChenPi 6g, HouPu 12g, ZhiKe 10g, WuLingZhi 12g, ChuanXiong 10g, DanShen 20g, YanHuSuo 20g, (3) for TCM syndrome of Deficiency of Stomach-Ying: NanShaShen 15g, MaiDong 12g, DiHuang 12g, DangGui15g, ShiHu 10g, BaiShao 10g, WuMei 15g, GanCao 6g.	Amoxicillin, Chinese Goldthread Rhizome, Colloidal Bismuth Pectin1, Domperidone	8 weeks	Not reported
Meng ZJ	10.3969/j.issn .1005-5304.2 006.04.028	1998-2005	2006	[27, 70]	135	75/60	Wei-Shu Decoction [HuangQi 45g, DangShen 15g, BaiZhu 15g, ZhiKe 10g, MaiDong 15g, NanShaShen 15g, DangGui15g, BaiShao 12g, HuangQi 10g, PuGongYing 15g, BanXie 6g, DanShen 30g, TianQi 5g, GanCao 10g]	Amoxicillin, Metronidazole, Colloidal Bismuth Pectin1, Domperidone	8 weeks	Not reported
Kan SY	10.3969/j.issn	1997-2005	2006	[31, 64]	110 (65/45)	70/40	Yang-Ying-Rong-Wei-Wan [DiHuang, BeiShaShen,	Vitacoenzyme	90 days	Not

	.0257-358X.2006.02.008						DangGui, ShouWuTeng, HuangLian, BaiShao, GouQiZi, MaiDong, BanXie, JiangHuang, BianDou, GanCao, MaiYa]	Tablets		reported
Zhao HB	10.3969/j.issn.1000-3649.2006.09.037	2001-2005	2006	[18, 58]	90 (52/38)	49/41	Wei-Ling-San [CaoGuo 70g, WuLingZhi 70g, RuXiang 65g, MoYao 65g, GuaLou 85g, BaiHuaSheSheCao 85g, HuangLian70g, BanXie 50g]	Sucralfate, Metronidazole	2 months	Not reported
Li JR	10.3969/j.issn.1000-1719.2005.02.018	2004	2005	[31, 51]	72	36/36	(1) For TCM syndrome of Weakness of Spleen and Stomach: HuangQi 15g, DangShen 15g, BaiZhu 10g, FuLing 10g, BaiShao 10g, GuiZhi 6g, GanCao 10g, ShengJiang 10g, DaZao 6, ShaRen 6g, (2) for TCM syndrome of Coke and Blood Stasis: BanXie 10g, ChenPi 6g, FuLing 10g, HouPu 12g, BaiZhu 15g, WuLingZhi 12g, ChuanXiong 10g, YanHuSuo 20g, SanLeng 10g, JiangHuang 10g, GanCao 10g, DanShen 20g, YiYiRen 10g, ShaRen 6g, (3) for TCM syndrome of Deficiency of Stomach-Ying: NanShaShen 15g, MaiDong 12g, DiHuang 12g, DangGui15g, BaiShao 10g, ShiHu 10g, WuMei 15g, GanCao 6g	Amoxicillin, Chinese Goldthread Rhizome, Colloidal Bismuth Pectin1, Domperidone	8 weeks	Not reported
Wang HY	10.3969/j.issn.1000-1719.2005.12.037	2005	2005	[26, 63]	130 (7 /56)	100/30	Shen-Ji-Yang-Wei Decoction [HuangQi 15g, NanShaShen 10g, BaiShao 15g, YanHuSuo 10g, DanShen 10g, BaiJi 8g, BeiMu15g, GanCao 5g]	Omeprazole, Amoxicillin, Metronidazole Bismuth Potassium Citrate Capsules, Amoxicillincapsule, Vitacoenzyme Tabletstablet, Domperidone tablet.	4 weeks	Not reported
Wei YQ	10.3969/j.issn.1004-745X.2005.12.067	1990-2003	2005	[31, 65]	90 (54/36)	54/36	TaiZiShen 50g, HuangQi 50g, FuLing 30g, BaiZhu 12g, DanShen 15g, JiangHuang 15g, MuGua 12g, WuMei 9g, ChaiHu 9g, BaiHuaSheSheCao 30g	Vitacoenzyme Tabletstablet, Folic Acidtablet, domperidone	6 months	Not reported
Gong DH	10.3969/j.issn.1672-951X.2004.12.008	1998-2004	2004	[16, 67]	100 (58/42)	50/50	HuangQi 15g, BaiZhu 10g, FuLing 10g, NanShaShen 15g, MaiDong 15g, E'Jiao 10g, PuGongYing 15g, BaiHuaSheSheCao 15g, WuLingZhi 10g, PuHuang 10g, ZhiKe 10g, ShanZha 10g	Patients with gastrectasia: Cisapride or Domperidone; patients with stomach-ache: Compound Belladonna Mixture, patients with anemia: Vitamin B and Folic Acid; patients with H.pylori infection: Amoxicillin, metronidazole, Colloidal Bismuth Pectin	2-4 months	Not reported
Wei BQ	10.3969/j.issn.0256-7415.2003.12.015	1998-2002	2003	No data	176 (95/81)	96/80	Wei-Ling Decoction [DangShen15g, FuLing, DanShen 15g, XiangFu 15g, JiaoSanXian 15g, PuGongYing 15g, GaoLiangJiang 10g, NvZhenZi 10g, BaiShao 10g, GuiZhi 10g, GanCao 6g, HuangQi 30g, BaiZhu 12g]		45 days	Not reported

https://doi.org/10.21010/ajtcam.v14i4.33

2: Int. CHD-WM vs. WM

Author	DOI/ Website	Duration of clinical trail	Year of publication	Age [range]	Participants	Number of Intervention/ Control	Intervention	Control	Duration of therapy	Adverse events
Fu HK	http://lib.cqvip.com/qk/93943A/201403/48935322.html	2010-2012	2014	[25, 69]	50 (19/31)	25/25	WM: Omeprazole, Amoxicillin, Clarithromycin CHD: DangShen 10g, DiHuang 10g, WuLingZhi 10g, PuHuang 10g, TaiZiShen 20g, GanCao 6g, CHD: HuangQi 30g, BaiZhu 12g, NanShaShen 15g, MaiDong 15g	Omeprazole, Amoxicillin, Clarithromycin	N/R	Not reported
Liu DX	10.3969/j.issn.1004-437X2014.01.055	2010-2012	2014	[33, 36]	80 (59/21)	40/40	WM: Omeprazole, Vatacoenayme, Tinidazole, Clarithromycin CHD: HuangQi 15g, DangShen 10g, BaiShao 10g, NanShaShen 10g, DangGui10g, PuHuang 10g, WuLingZhi 10g, PuHuang 10g, ZhiGanCao 5g	Omeprazole, Vatacoenayme, Tinidazole, Clarithromycin	2 months	Not reported
Shan Q	10.3969/j.issn.1004-7484(x).2014.06.038	2011-2013	2014	[38, 42]	112 (31/27)	54/58	WM: Thiazole, PPI, Triple therapy or Quadruple therapy CHD: for patients with stagnation of liver-QI and stomach-QI: Chai-Hu-Shu-Gan-San; for patients with epigastralgia: Hua-Gan-Jian-He-Zuo-Jin-Wan; for patients with damp heat in the spleen and the stomach: Huang-Lian-Wen-Dan Decoction; for patients with weakness of the spleen and the stomach: Liu-Jun-Zi Decoction; for patients with Stomach yin deficiency: NanShaShen, MaiDong Decoction; patients with stomach and blood stasis: DanShen Decoction	Thiazole, PPI, Triple therapy or Quadruple therapy	6 months	Not reported
Wang J	10.3969/j.issn.1009-4393.2013.6.109	2011-2012	2013	[22, 79]	128 (74/54)	64/64	WM: Vatacoenayme, Bismuth Biskalcitrate, Amoxicillin, Tinidazole, Domperidone CHD: DangShen 20g, BaiZhu 15g, HuangQi 20g, BaiShao 15g, FuLing 15g, DanShen 20g, DangGui 12g, YanHuSuo 15g, ShaRen 10g, TianQi 3g, E'Zhu 10g, MuXiang 10g, ChaiHu 10g	Vatacoenayme, Bismuth Biskalcitrate, Amoxicillin, Tinidazole, Domperidone	2 months	Not reported
Han XF	http://d.wanfangdata.com.cn/Periodical/jkbd-x201308126	2010-2012	2013	[37, 78]	40 (19/27)	20/20	WM: Vatacoenayme, Amoxicillin CHD: Yi-Wei-Suo-Xing-Wei-Yan Decoction: DangShen 30g, PuGongYing 30g, ChuanXiong 10g, HuangQi30g, E'Zhu 10g, JiNeiJin 15g, TianQi 3g, DanShen 20g, DaHuang 5g, HouPu 5g, YanHuSuo 15g	Vatacoenayme, Amoxicillin	4 months	Not reported
Li SQ	doi：10.3969/j.issn1007-8231.2012.11.067	2011	2012	[30, 65]	59 (41/17)	29/29	WM: Vatacoenayme, Colloidal Bismuth, Amoxicillin, Tinidazole, Domperidone CHD: HuangQi 30g, DangShen 20g, BaiZhu 10, FuLing 10g, BaiShao 15g, MaiDong 15g, ShiHu 15g, DiHuang 30g, E'Zhu 15g, FoShou 15g, QingDai 3g, ZhiGanCao 9g	Vatacoenayme, Colloidal Bismuth, Amoxicillin, Tinidazole, Domperidone	4 weeks	Not reported

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Zhang WH	http://d.wanfangdata.com.cn/Periodical/jkbd-z201208150	2005-2010	2012	[28, 72]	120	68/52	WM: Tinidazole, Clarithromycin, Domperidone, Vatacoenayme CHD: NanShaShen 10g, MaiDong 10g, ShiHu 10g, ZeXie 10g, BaiZhu 10g, BaiShao 10g, TaiZiShen 15g, DanShen 15g, HuangQi 12g, ShanYao 15g, FoShou 6g, MuXiang 6g, ShaRen 5g, ShengMa 6g, Dihuang 10g	Tinidazole, Clarithromycin, Domperidone, Vatacoenayme	2 months	Not reported
Wang XF	http://www.cqvip.com/QK/87361X/201103/1003588945.html	2009-2010	2011	[19, 72]	136 (78/58)	68/68	CHD: Wen-Yang-Hua-Tan Decoction: HuangQi 50g, YiYiRen 20g, DangShen 20g, BaiZhu 15g, FuLing 15g, GuiPi 10g, DingXiangZhi 10g, HuoXiang 10g, PeiLan 10g, ShaRen 5g WM: Vatacoenayme, Omeprazole, Metronidazole, Amoxicillin	Vatacoenayme, Omeprazole, Metronidazole, Amoxicillin	6-8 weeks	control: 12 patients with gastrointestinal adverse reaction, such as nausea, vomiting, abdominal distention; intervention: six patients with minor gastrointestinal adverse reaction
Kuang YJ	doi:10.3969/j.issn.1009-4393.2011.19.101	2008-2010	2011	[21, 67]	120 (76/44)	60/60	WM: Bismuth Biskalcitrate, Omeprazole, Clarithromycin, Amoxicillin, Domperidone CHD: TianQi 3g, ZhiGanCao 5g, WuZhuYu 5g, ShaRen 6g, HuangLian 6g, NanShaShen 6g, DangGui 10g, BaiZhu 10g, HouPu 10g, HuangQi 15g, FuLing 15g, DangShen 20g, ShanYou 20g	Bismuth Biskalcitrate, Omeprazole, Clarithromycin, Amoxicillin, Domperidone	N/R	no patient with adverse reaction both in control and intervention
Liu HR	http://www.cqvip.com/QK/71135X/201107/34896346.html	2003-2007	2010	[30, 63]	100 (59/41)	50/50	WM: Omeprazole, Clarithromycin, Tinidazole; CHD: Wei-Shu-Jian-Ji [ChaiHu, BaiShao, GanCao, ZhiKe, DaHuang, PuGongYing, FuLing, BaiZhu, ChuanLianZi, YanHuSuo, LiYa, DanShen]	Omeprazole, Clarithromycin, Tinidazole	6 months	Not reported
Gao Z	http://www.cqvip.com/Main/Detail.aspx?id=31422276	1999-2007	2009	[25, 72]	83 (54/29)	46/37	WM: Colloidal Bismuth Pectin Vitacoenzyme Compound Pepsin; CHD: Zi-Yin-Hua-Yu-Ning-Wei Decoction [TaiZiShen 20g, BaiShao 20g, ShiHu 15g, WuMei 15g, GanCao 10g, E'Zhu 10g, ZiSuGeng 10g, TianQi 6g, HuangYaoZi 12g, ChuanLianZi 9g]	Colloidal Bismuth Pectin Vitacoenzyme Compound Pepsin;	12 months	Not reported
Lei CH	http://www.c	2009	2009	[33, 65]	68	34/34	WM: Metronidazole, Folic Acid;	Metronidazole, Folic	24 weeks	Not

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	nki.com.cn/Article/CJFDTotal-SYBD200904007.htm						CHD: Si-Jun-Zi Decoction [RenShen 9g, BaiZhu 9g, FuLing 9g, WuLingZhi 8g, ChuanXiong 8g, BaiHuaSheSheCao 10g, GanCao 6g]	Acid		reported
Ma J	http://www.cqvip.com/Main/Detail.aspx?id=30648302	2007-2008	2009	[30, 65]	60 (31/29)	30/30	WM: Omeprazole, Clarithromycin, Amoxicillin; CHD:Jian-Pi-Yi-Wei Decoction [HuangQi 20g, Dangshen 20g, BaiZhu 15g, GuiZhi 10g, DanShen 15g, ChiShao15g, ShanZha 10g, BaiShao 15g, E'Zhu 10g, GanCao 5g]	Omeprazole, Clarithromycin, Amoxicillin, Vitamin E, Carotene	3 months	Not reported
Huang GC	10.3969/j.issn.1672-2779.2009.04.071	2004-2007	2009	[30, 81]	85 (58/27)	45/40	WM: Colloidal Bismuth Pectin capsule; CHD: Ban-Xia-Xie-Xin Decoction [BanXie 10g, Dangshen 20g, HuangLian6g, HuangQi 10g, GanJiang 5g, GanCao 6g, PuGongYing 15g, ZhiKe 10g, MoYuGu 15g, BaiHuaSheSheCao 15g] CHD: for TCM syndrome of Weakness of Spleen and Stomach: Dangshen, HuangQi, ShanYao, GanCao, BaiZhu, GanJiang, NanShaShen, DaZao; for TCM syndrome of Liver Stomach Disharmony: ChaiHu, MuXiang, FoShou, BaiShao, NanShaShen, MaiDong, YuZhu, HuangLian, ShiHu, GanCao, YanHuSuo, Reed Rhizome; for TCM syndrome of Stagnation of Phlegm: ChenPi, FuLing, BanXie, BaiZhu, HouPu, HuangQi, GanJiang, GanCao; for TCM syndrome of Damp-Heat in Spleen and Stomach: HuangLian, HuangQi, PuGongYing, BanXie, ZhuRu, FuLing, YiYiRen, ZeXie, FoShou, ChenPi, ZhiKe; for TCM syndrome of Stomach Collateral Stasis: YanHuSuo, MoYao, WuLingZhi, CaoGuo, DanShen, ChiShao, E'Zhu, PuHuang, TaoRen.	Colloidal Bismuth Pectin capsule	12 weeks	Not reported
Song FL	http://lib.cqvip.com/qk/91070A/200903/29592636.html	2005-2007	2009	[33, 65]	68 (41/27)	34/34	WM: Metronidazole, Folic Acid; CHD: Jia-Wei-Si-Jun-Zi Decoction [Dangshen 9g, BaiZhu 9g, FuLing 9g, WuLingZhi 8g, ChuanXiong 8g, BaiHuaSheSheCao 6g, GanCao 6g]	Metronidazole, Folic Acid	24 weeks	Not reported
Zhang DF	10.3969/j.issn.1001-6910.2008.03.016	1999-2006	2008	[45, 70]	70 (41/29)	36/34	WM: Omeprazole capsule, Amoxicillin capsule, Metronidazole tablet, Folic Acid; CHD: Dan-shen-Yin plus Chai-Shao-Liu-Jun-Zi Decoction [HuangQi 3g, RenShen 6g, FuLingg, BaiZhu 6g, DanShen 3g, DangGui12g, TanXiang 6g, ShaRen 6g, BanXie 6g, MuXiang 6g, BaiShao 12g, ChaiHu 10g, HuangQi 12g, GanCao 3g]	Omeprazole capsule, Amoxicillin capsule, Metronidazole tablet, Folic Acid	60-150 days	Not reported
Shen Y	10.3969/j.issn.1001-9448.2007.03.068	2000-2006	2007	[17, 75]	132 (82/50)	69/63	WM: Bismuth Potassium Citrate Capsules, Domperidone, Weilesheng tablet, Cimetidine, metronidazole, Amoxicillin CHD: Dan-Shen-Yin plus Shi-Xiao-San [DanShen 30g, YanHuSuo 10g, TanXiang 10g, ShaRen 5g,	Bismuth Potassium Citrate Capsules, Domperidone, Weilesheng tablet, Cimetidine,	3 months	two cases reported rash in intervention

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							ZiSuGeng 10g, JuLuo 10g, DaHuang 5g, GanCao 3g, PuHuang 10g, WuLingZhi 10g]	metronidazole, Amoxicillin		
Xiang SY	10.3969/j.issn.1671-4040.2007.05.007	2007	2007	[37, 68]	130 (72/58)	80/50	WM: Sucralfate tablet, Mosapride, Folic Acid; CHD: Fu-Fang-Wu-Shen Decoction [Dangshen 15g, NanShaShen 12g, XuanShen 10g, DanShen 10g, KuShen 10g, MaiDong 15g, HuangJing 10g, ChuanXiong 10g, HuangLian 10g, HuangQi 12g, ShiHu 15g, JinFeiCao 10g]	Sucralfate tablet, Mosapride, Folic Acid	3 months	Not reported
Zhou AX	http://192.168.89.197:8012/ArticleDetail.aspx?id=21906480	2004-2006	2006	[29, 71]	60 (30/30)	30/30	WM: one chosen from Omeprazole, Lansoprazole, Bismuth Potassium Citrate, plus one chosen from Clarithromycin, Amoxicillin, Metronidazole CHD: Bu-Yi-Ha-Yu Decoction [HuangQi 30g, TaiZiShen 30g, NanShaShen 20g, MaiDong 20g, DangGui20g, DiHuang 30g, E'Zhu 10g, HongHua 6g, MoYao 10g, BaiHuaSheSheCao 30g]	One chosen from Omeprazole, Lansoprazole, Bismuth Potassium Citrate, plus one chosen from Clarithromycin, Amoxicillin, Metronidazole.	2 months	Not reported
Wang HB	10.3870/j.issn.1004-0781.2003.11.010	1999-2000	2003	54 patients >40, 11 patients <40:	65	35/30	WM: Colloidal Bismuth Pectin, Amoxicillin, Furazolidone; CHD: Wei-Fu-Jian-Ji [TaoRen 10g, HongHua 10g, ChuanXiong 10g, ChiShao10g, PuGongYing 10g, MuXiang 10g, GanCao 10g, HuangQi 20g, Dangshen 15g]	Colloidal Bismuth Pectin, Amoxicillin, Furazolidone	4 weeks	Not reported
Yue WJ	10.3760/cma.j.issn.1008-6706.2003.11.055	1998-2003	2003	[31, 79]	85 (49/36)	58/27	WM: Colloidal Bismuth Pectin capsule, Tinidazole tablet, Vitamin C tablet, Folic Acid tablet; CHD: Xiang-Sha-Liu-Jun-Zi Decoction [XiangFu 15g, ShaRen 10g, RenShen 15g, BaiZhu 20g, FuLing 15g, GanCao 10g, ChenPi 10g, BanXie 10g] CHD: Chu-Pi-Yang-Wei Decoction: [Dangshen l5g, FuLing 15g, E'Zhu l5g, WuZhuYu 6g, MuXiang 9g, GanCao 6g, HuangJing 15g , ShanYao 30g, ShaRen 6g, HuangLian 6g, BaiJiangCao 30g]	Colloidal Bismuth Pectin capsule, Tinidazole tablet, Vitamin C tablet, Folic Acid tablet	6 weeks	Not reported

https://doi.org/10.21010/ajtcam.v14i4.33

Supplementary Table 3: List of traditional Chinese herbs used in included studies

Pinyin Name	Chinese Name	Latin Name	English Name
BaiHe	百合	*Lilium brownii var. viridulum*	Greenish lily bulb
BaiHuaSheSheCao	白花蛇舌草	*Hedyotis diffusa* Spreng.	Spreading hedyotis herb
BaiJi	白及	*Bletilla striata* (Thunb.) Rchb.f.	Common bletilla tuber
BaiJiangCao	败酱草	*Hlaspi arvense* L	Dahurian patrinia herb
BaiShao	白芍	*Paeonia lactiflora* Pall.	White peony root
BaiZhu	白术	*Atractylodes macrocephala* Koidz	Largehead atractylodes rhizome
BanXie	半夏	*Pinellia ternata* (Thunb.) Breit.	Ternate pinellia
BeiMu	贝母	*Fritillaria cirrhosa* D.Don	Fritillaria
BeiShaShen	北沙参	*Glehnia littoralis* F.Schmidt ex Miq.	Coastal glehnia root
BianDou	扁豆	*Lablab purpureus* (L.) Sweet	Dolichos lablab
CaoGuo	草果	*Amomum tsao-ko* Crevost & Lemarié	Tsao-ko amomum fruit
ChaiHu	柴胡	*Bupleurum chinense* DC.	Chinese thorowax root
ChenPi	陈皮	*Clausena lansium* (Lour.) Skeels	Tangerine peel
ChiShao	赤芍	*Paeonia anomala subsp. veitchii (Lynch) D.Y.Hong & K.Y.Pan*	Red peony root
ChuanXiong	川芎	*Cortia striata* (DC.) Leute	Szechwan lovage rhizome
ChuanLianZi	川楝子	*Melia toosendan* Siebold & Zucc	Szechwan chinaberry fruit
DaHuang	大黄	*Rheum palmatum* L.	Rhubarb
DangGui	当归	*Angelica sinensis* (Oliv.) Diels	Chinese angelica

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DangShen	党参	*Codonopsis pilosula* (Franch.) Nannf.	Codonopsis pilosula
DanShen	丹参	*Salvia miltiorrhiza Bunge*	Dan-shen root
DaZao	大枣	*Ziziphus jujuba* Mill	Common jujube
DiHuang	地黄	*Rehmannia glutinosa* (Gaetn) Libosch. ex Fisch. et Mey	Rehmannia root
DingXiangZhi	丁香枝	*Syzygium aromaticum* (L.) Merr.Et Perry	Clovetree twig
E'Jiao	阿胶	*Colla Corii Aaini*	Ass-hide gelatin
E'Zhu	莪术	*Curcuma zedoaria* (Christm.) Roscoe	Rhizoma curcumae
FoShou	佛手	*Citrus medica var. sarcodactylus* (Siebold ex Hoola van Nooten) Swingle	Finger citron fruit
FuLing	茯苓	*Poria cocos* Wolf [Fungi]	Indian buead
GanCao	甘草	*Glycyrrhiza uralensis* Fisch.	Liquorice root
GanJiang	干姜	*Zingiber officinale* Roscoe	Dried ginger
GaoLiangJiang	高良姜	*Alpinia officinarum* Hance	Lesser galangal rhizome
GouQiZi	枸杞子	*Lycium barbarum* L.	Barbury wolfberry fruit
GuaLou	瓜蒌	*Trichosanthes kirilowii* Maxim	Mongolian snakegourd fruit
GuiZhi	桂枝	*Cinnamomum cassia* (L.) J.Presl	Cassiabarktree twig
HongHua	红花	*Carthamus tinctorius* L.	Safflower
HouPu	厚朴	*Citrus grandis* (L.) Osbeck	Officinal magnolia bark
HuangJing	黄精	*Polygonatum sibiricum* F.Delaroche	Siberian solomonseal rhizome
HuangLian	黄连	*Coptis chinensis* Franch.	Chinese goldthread rhizome
HuangQi	黄芪	*Astragalus membranaceus* (Fisch.) Bunge	Astragalus membranaceus

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HuangQin	黄芩	*Scutellaria* Linn.	Radix scutellariae
HuangYaoZi	黄药子	*Dioscorea bulbifera* L.	Airpotato yam rhizome
HuoXiang	藿香	*Agastache rugosa* (Fisch. & C.A.Mey.) Kuntze	Agastache rugosus
JiangHuang	姜黄	*Curcuma longa* L.	Turmeric rhizome
JiaoSanXian	焦三仙	*Hordeum vulgare* L Plus *Crataegus pinnatifida* Bunge Plus *Massa Medicata* Fermentata	Stir-baking fructus hordei germinatus et crataegt et massa fer-mentata medicinalis
JiNeiJin	鸡内金	Gallus gallus domesticus Brisson	Corium stomachichum galli
JinFeiCao	金沸草	*Inula japonica* Thunb.	Inula flower
JuLuo	桔络	*Citrus reticulata* Blanco	Tangerine pith
KuShen	苦参	*Sophora flavescens* Aiton	Lightyellow sophora root
LianQiao	连翘	*Forsythia suspensa* (Thunb.) Vahl	Weeping forsythia fruit
LiChang	鳢肠	*Eclipta prostrata* (L.) L.	Eclipta prostrata
LiYa	粟芽	*Setaria italica* (L.) P.Beauv.	Foxtail millet sprout
MaiDong	麦冬	*Ophiopogon japonicus* (Thunb.) Ker Gawl.	Dwarf lilyturf root tuber
MaiYa	麦芽	*Hordeum vulgare* L	Malt
MoYao	没药	*Commiphora myrrha* (Nees) Engl.	Myrrh
MoYuGu	墨鱼骨	*Sepia esculenta Hoyle*	Cuttlebone
MuGua	木瓜	*Chaenomeles chinensis* (Dum.Cours.) Koehne	Common floweringquine fruit
MuXiang	木香	*Rosa banksiae* R.Br.	Costusroot
NanShaShen	南沙参	*Adenophora tetraphylla* (Thunb.) Fisch.	Upright ladybell root
NvZhenZi	女贞子	*Ligustrum lucidum* W.T.Aiton	Glossy privet fruit

PaoShanJia	炮山甲	*Squama Manis*	Parched pangolin scales
PeiLan	佩兰	*Eupatorium fortunei* Turcz.	Eupatorium fortunei
PuGongYing	蒲公英	*Taraxacum mongolicum* Hand.-Mazz.	Mongolian dandelion herb
PuHuang	蒲黄	*Typha angustifolia* L.	Cattail pollen
QingDai	青黛	*Baphicacanthus cusia* (Nees) Bremek	Indigo naturalis
RenShen	人参	*Panax ginseng* C.A.Mey.	Ginseng
RouDoukou	肉豆蔻	*Myristica fragrans* Houtt.	Fructus amomi rotundus
RuXiang	乳香	*Boswellia carteri* Birdw.	Frankincense
SanLeng	三棱	*Sparganium stoloniferum* (Buch.-Ham. ex Graebn.) Buch.-Ham. ex Juz	Common burreed tuber
ShanYao	山药	*Dioscorea oppositifolia* L.	Common yam rhizome
ShanZha	山楂	*Crataegus scabrifolia* (Franch.) Rehder	Chinese hawthorn fruit
ShaRen	砂仁	*Amomum villosum* Lour.	Villous amonmum fruit
ShengJiang	生姜	*Zingiber officinale* Roscoe	Fresh ginger
ShengMa	升麻	*Cimicifuga foetida* L.	Rhizoma cimicifugae
ShiHu	石斛	*Dendrobium catenatum* Lindl	Noble dendrobium stem herb
ShouWuTeng	首乌藤	*Fallopia multiflora* (Thunb.) Harald	Tuber fleeceflower stem and leaf
TaiYangHua	太阳花	*Portulaca grandiflora*	Portulaca grandiflora
TaiZiShen	太子参	*Pseudostellaria heterophylla* (Miq.) Pax	Pseudostellaria root
TanXiang	檀香	*Gaultheria fragrantissima Wall*	Sandalwood
TaoRen	桃仁	*Prunus persica* (L.) Batsch	Peach seed

Tianqi	田七	*Panax pseudoginseng var. notoginseng* (Burkill) G.Hoo & C.L.Tseng	Pseudo-ginseng
TongHuaGen	通花根	*Tetrapanax papyrifer* (Hook.) K.Koch	Ricepaperplant
WaLengZi	瓦楞子	*Concha Arcae*	Arc shell
WuLingZhi	五灵脂	*Faeces Trogopterpri*	Trogopterus dung
WuMei	乌梅	*Prunus mume* (Siebold) Siebold & Zucc.	Smoked plum
WuYao	乌药	*Lindera aggregata* (Sims) Kosterm.	Combined spicebush root
WuZao	乌枣	*Diospyros lotus* L.	Smoked jujube
WuZhiMaoTao	五指毛桃	*Ficus simplicissima* Lour.	Radix fici simplicissimae
WuZhuYu	吴茱萸	*Tetradium ruticarpum* (A.Juss.) T.G.Hartley	Medicinal evodia immature fruit
XiangFu	香附	*Cyperus rotundus* L.	Nutgrass galingale rhizome
XuanShen	玄参	*Scrophularia oldhamii* Oliv.	Figwort root
YanHuSuo	延胡索	*Corydalis yanhusuo*	Yanhusuo tuber
YiYiRen	薏苡仁	*Coix lacryma-jobi* L.	Ma-yuen jobstears seed
YuZhu	玉竹	*Polygonatum odoratum* (Mill.) Druce	Fragrant solomonseal rhizome
ZaoCi	皂刺	*Gleditsia sinensis* Lam.	Spina gleditsiae
ZeXie	泽泻	*Alisma plantago-aquatica* L.	Rhizoma alismatis
ZhiGanCao	炙甘草	*Glycyrrhiza uralensis* Fisch.	Prepared liquorice root
ZhiKe	枳壳	*Citrus × aurantium* L.	Submature bitter orange
ZhuRu	竹茹	*Sinocalamus beecheyanus* (Munro) McClure	Bamboo shavings
ZiSuGeng	紫苏梗	*Perilla frutescens* (L.) Britton	Caulis perillae acutae

Eradication of H. pylori

There were 12 trials reporting the eradication rate of *H. pylori*. Remission of *H. pylori* infection was not achieved in

https://doi.org/10.21010/ajtcam.v14i4.33

121 (21.8%) of 554 patients randomized to receive CHD (alone or integrated with WM), compared with 180 (38.2%) of 471 patients received WM (RR=1.29; 95% CI 1.11-1.50) with significant heterogeneity between studies (I^2=71%) (Figure 2). There was statistically significant funnel plot asymmetry (Egger's test p=0.044), suggesting evidence of publication bias or other small study effects.

In subgroup of CHD monotherapy versus WM, six trials reported the eradication rate of *H. pylori*. There was no significant difference between CHD and WM in *H. pylori* eradication (RR=1.12, 95% CI 0.95-1.32) (Figure 2), with significant heterogeneity between studies (I^2=59%). However, the pooled data suggested that CHD with WM had beneficial effect over WM (RR=1.52, 95% CI 1.14-2.02), with significant heterogeneity between studies (I^2=76%).

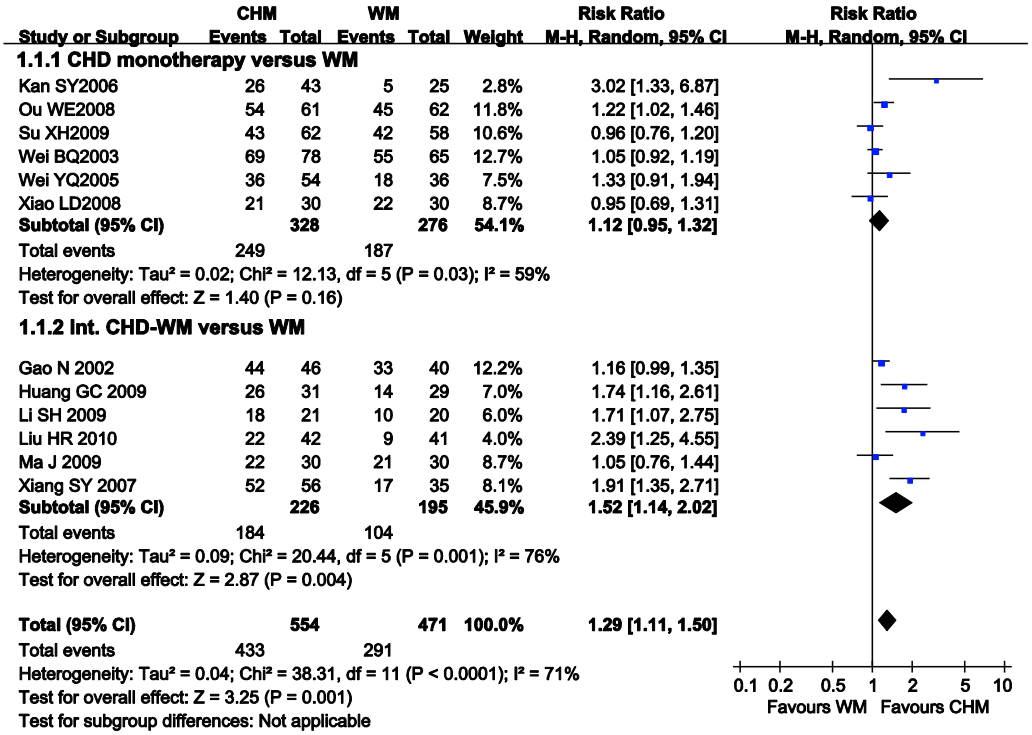

Figure 2: Efficacy of CHD compared with WM in eradication of *H. pylori*

Note: CHD, Chinese herbal decoction; WM, western medicine; Int. CHD-WM, integrated Chinese herbal decoction and western medicine; 95% CI, 95% confidence interval. Each point on the figure represents a relative risk (RR). The diamond represents the pooled estimate of effect, as calculated according to the random effects model. RR<1 means numerically lower response rate than WM, and RR>1 numerically higher response rate than WM. 95% CI doesn't include the number 1 means statistical difference between the two groups.

Clinical manifestations improvement

In total, 38 trials compared CHD (alone or integrated with WM) with WM involving 3,812 patients reported clinical manifestations improvement rate. There are 173 (8.3%) of 2,091 assigned to CHD (alone or integrated with WM) who failed to improve clinical manifestations, compared with 503 (28.8%) of 1,747 patients allocated to WM (RR=1.28; 95% CI 1.22-1.34), without significant heterogeneity between studies (I^2=44%) (Figure 3). Evidence of publication bias was observed (Egger's test p=0.000).

In subgroup of CHD monotherapy versus WM, 25 studies reported the clinical manifestations improvement rate. The pooled data suggested that CHD had beneficial effect over WM (RR=1.28, 95% CI 1.22-1.35), without significant heterogeneity between studies (I^2=34%). While Int. CHD-WM was found to be beneficial over WM alone (RR=1.27, 95% CI 1.16-1.39), with significant heterogeneity between studies (I^2=60%). There was statistically significant funnel plot asymmetry in the two subgroups (Egger's test p=0.0017, p=0.0019, respectively), suggesting evidence of publication bias.

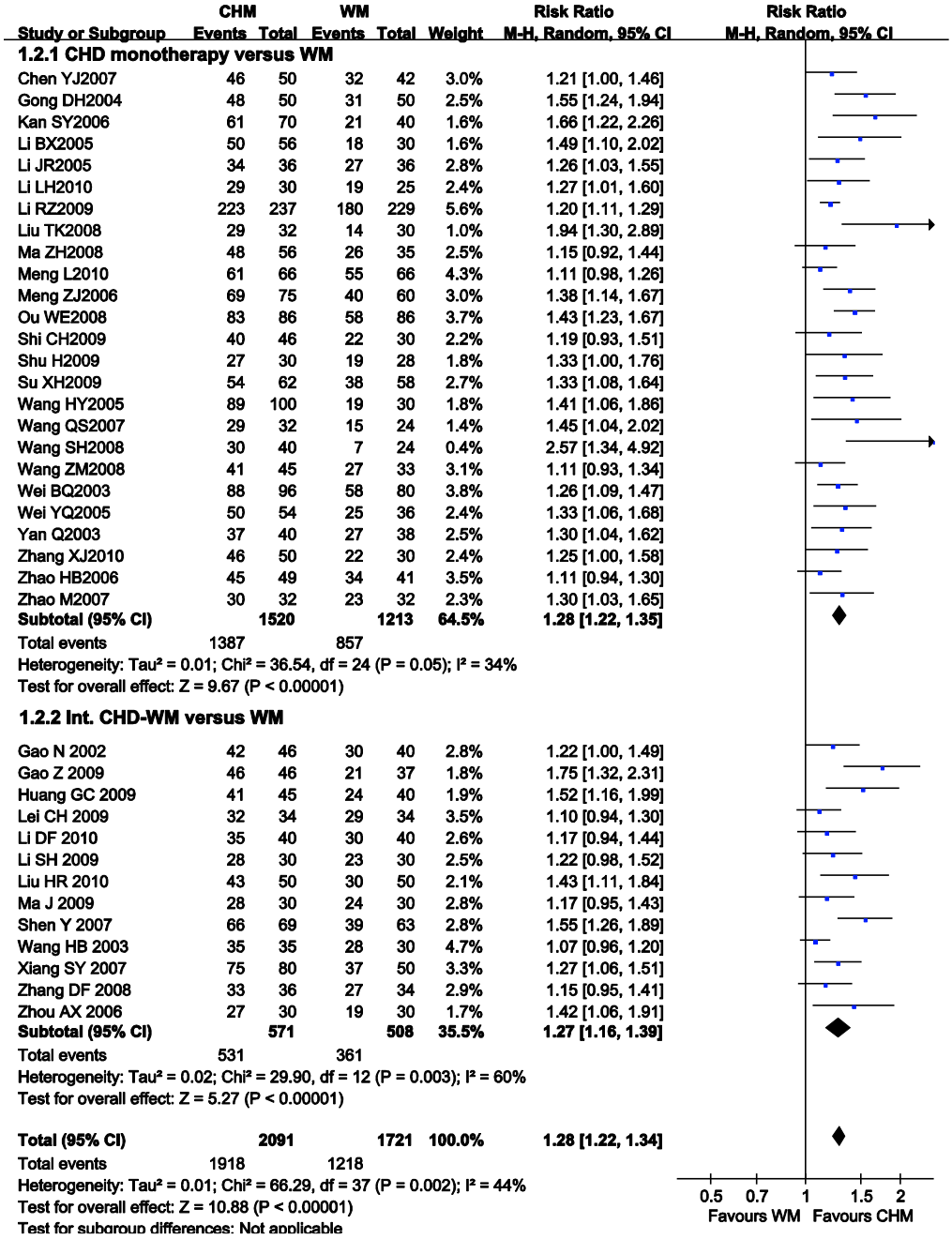

Figure 3: Efficacy of CHD compared with WM in clinical manifestations improvement

Note: CHD, Chinese herbal decoction; WM, western medicine; Int. CHD-WM, integrated Chinese herbal decoction and western medicine; 95% CI, 95% confidence interval. Each point on the figure represents a relative risk (RR). The diamond represents the pooled estimate of effect, as calculated according to the random effects model. RR<1 means numerically lower response rate than WM, and RR>1 numerically higher response rate than WM. 95% CI doesn't include the number 1 means statistical difference between the two groups.

Pathological improvement

Totally, 20 trials compared CHD (alone or integrated with WM) with WM in 1,959 patients reported pathological improvement. 154 (14.9%) of 1034 patients using CHD (alone or integrated with WM) failed to improve pathological change, compared with 360 (46.0%) of 925 patients using WM (RR=1.42; 95% CI 1.30-1.54), without significant heterogeneity between studies (I^2=48%) (Figure 4). Evidence of publication bias was observed (Egger's test p=0.002).

In subgroup of CHD monotherapy versus WM, 13 studies reported pathological improvement rate. The result suggested that CHD had beneficial effect over WM (RR=1.33, 95% CI 1.22-1.45), without significant heterogeneity between studies (I^2=36%). In subgroup of Int. CHD-WM versus WM, Int. CHD-WM was found to be beneficial over

WM (RR=1.57, 95% CI 1.37-1.80), without significant heterogeneity between studies (I^2=11%). Statistically significant funnel plot asymmetry was only found in subgroup of CHD monotherapy versus WM (Egger's test p=0.016), suggesting evidence of publication bias or other small study effects.

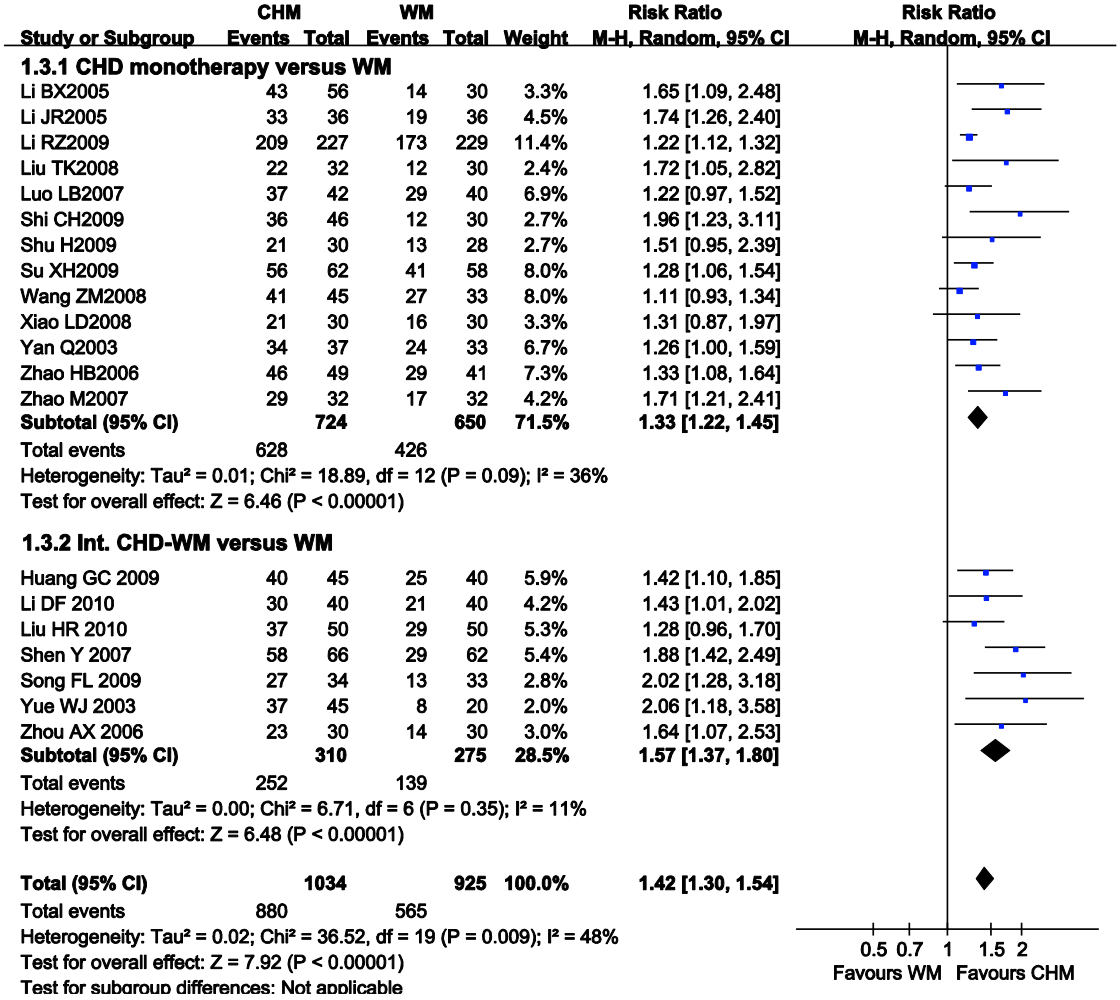

Figure 4: Efficacy of CHD compared with WM in pathological improvement

Note: CHD, Chinese herbal decoction; WM, western medicine; Int. CHD-WM, integrated Chinese herbal decoction and western medicine; 95% CI, 95% confidence interval. Each point on the figure represents a relative risk (RR). The diamond represents the pooled estimate of effect, as calculated according to the random effects model. RR<1 means numerically lower response rate than WM, and RR>1 numerically higher response rate than WM. 95% CI doesn't include the number 1 means statistical difference between the two group*Adverse events*

Only minor side effects, such as urticarial, rash, and slight gastrointestinal discomfort, were found in CHD group (shown in Supplementary Table 2). There are no statistical differences in side effects between CHD (alone or with WM) and WM.

Sensitivity analysis

In order to evaluate the robustness of outcomes and identify sources of heterogeneity, we conducted prespecified sensitivity analyses. Totally 25 RCTs are at moderate risk of bias, 18 are at high risk of bias. In subgroup of CHD monotherapy the number is 15 (moderate) and six (high), while in subgroup of Int. CHD-WM the number is 10 (moderate) and 11 (high) (see Supplementary Table 1). The results were similar in direction and magnitude to the primary results expect the eradication rate of *H. pylori*, suggesting the robustness of most results in this study. However heterogeneity between trials still existed in the some outcomes (Table 1).

https://doi.org/10.21010/ajtcam.v14i4.33

Table 1: Sensitivity analyses of efficacy of CHM compared with WM in AG

	Number of studies	*Number of subjects*	*RR*	*95% CI*	*I^2 value*
Eradication rate of *H. pylori*					
CHM (alone or integrated with WM) versus WM	5	544	1.16	[0.96, 1.41]	66%
CHM versus WM	5	544	1.16	[0.96, 1.41]	66%
Int. CHM-WM versus WM	0	0	N/A	N/A	N/A
Clinical manifestations improvement					
CHM (alone or integrated with WM) versus WM	20	2,213	1.27	[1.22, 1.33]	12%
CHM versus WM	16	1,939	1.29	[1.23, 1.36]	10%
Int. CHM-WM versus WM	4	274	1.18	[1.07, 1.31]	0%
Pathological improvement					
CHM (alone or integrated with WM) versus WM	12	1,284	1.44	[1.27, 1.63]	60%
CHM versus WM	9	1,092	1.35	[1.20, 1.52]	53%
Int. CHM-WM versus WM	3	192	1.87	[1.42, 2.45]	0%

Note: N/A, not applicable; AG, atrophic gastritis; CHM, Chinese herbal medicine; WM, western medicine; Int. CHM-WM, integrated Chinese herbal medicine and western medicine; RR, relative risk; CI, confidence interval.

Discussion

Herbal decoction is a concentrated herbal tea in which raw roots, berries and barks are lightly simmered for hours to extract the useful constituents. Compared with Chinese herbal patent medicines, which is the ready-made pills or capsules of herbal extracts as products of modern pharmaceutical industry, CHD is considered to have more advantages such as flexibility in treatment and strictly following the basic TCM theory of *Bianzheng Lunzhi* strictly. Our study is the first systematic review and meta-analysis evaluating the efficacy and safety of all kinds of decoctions in the treatment of AG according to TCM symptom types. The results demonstrated that: 1) CHD may be more effective than WM in ameliorating clinical manifestations of AG; 2) CHD may be more effective than WM in reverting the precancerous lesions of AG; 3) CHD with WM may be more effective than WM in reverting the precancerous lesion of AG. Evidence from sensitivity analyses revealed that the primary results were relatively stable. However, similar conclusions cannot be drawn in the *H. pylori* eradication rate because of the significant heterogeneity between studies (I^2＞50%) and low robustness confirmed by sensitivity analysis. The source of the significant heterogeneity was failed to be identified by sensitivity analysis and subgroup analysis.

Our findings supported the clinical use of CHD for the alleviation of AG-related symptoms and pathologic change, which is consistent with the evidence from previous experimental studies. Pathologic changes and clinical symptoms of AG are mainly caused by *H. pylori*-related chronic inflammation in human gastric epithelial cells. Some herbs inhibits the generation of reactive oxygen species (ROS) prostaglandin E (2), cyclooxygenase-2 (COX-2), and interleukin (IL)-8 (Wang et al., 2012; Yu et al.,2013; Zaidi et al., 2012), and the strong anti-inflammatory activity can effectively protect gastric epithelial cells from gastric ulcer and cancer. Some herbs, such as *Abrus cantoniensis* Hance, have potent anti-*H. pylori* activity (Li et al.,2005; Safavi et al., 2015). However, the clinical efficacy of CHD to eradicate *H. pylori* in AG patients could not be concluded in the present study. We hypothesized the clinical and pathologic improvement of AG patients were more likely to be caused by the strong activity of CHD to inhibit *H. pylori*-related inflammation, than the eradication of *H. pylori* itself. Hence, we recommended that CHD be used as an adjunctive therapy to WM, but not used as an alternative to antibiotics for *H. pylori* eradication.

We included various decoctions for treating different TCM symptom types related to AG, and used the modified Jadad scale with a new scoring item of *Bianzheng Lunzhi*. This study design made our research strictly follow the TCM therapeutic theory. The basic therapeutic theory of *Bianzheng Lunzhi* is fundamentally different from that of WM. In the *Bianzheng Lunzhi* theory, a TCM physician should take the body, mind and spirit into account to decide which symptom type (not a “disease”) each patient belongs to (Chen et al., 2003). Based on TCM syndrome differentiation, diseases should be further classified into different clinical types for therapy. Hence, different kinds of decoctions can be used, and dosage and/or formula in a certain decoction can be added or subtracted according to individual's symptom types and changing states of disease. The personalized therapy according to the symptom type differentiation is the

guarantee of its efficacy and should be integrated into clinical trial design (Flower et al., 2012). Unlike previous studies focusing on a certain herb or decoction, our study adequately considered this individual-based therapeutic features, and made an overall evaluation of all kinds of prescriptions such as *Chai-Hu-Shu-Gan* decoction, *Shan-Jia-Yu-Wei* decoction, *Jian-Pi-Yi-Wei* decoction, and *Gan-Cao-Xie-Xin* decoction for various TCM symptom types.

Limitations of this review are as follows. Firstly, all the 42 articles that met the eligible criteria were at moderate to high risk of bias. Although sensitivity analyses excluding studies at high risk of bias found that the results were relatively stable, potential bias would exaggerate the efficacy to some extent (Kjaergard et al., 2001). Secondly, heterogeneity was observed in some results, especially the results of eradication rate of *H. pylori.* However, source of heterogeneity was failed to be identified by sensitivity analysis and subgroup analysis. Thirdly, publication bias, which might come from language bias, would potentially compromise the validity of some results and led to optimistic outcomes for treatment. Fourthly, our findings provided insufficient precision in the correlation between medical herbs and clinical outcomes. In fact, practitioners of Chinese medicine always prescribe mixtures of plants (decoction) instead of single plant as therapy. Therefore most RCTs regarding traditional Chinese medicine for atrophic gastritis is designed to evaluate the efficacy of decoctions. It is hard for us to evaluate the efficacy of certain plant for gastritis management using the meta-analysis. Last but not least, the herbs mentioned in all the included studies were not validated taxonomically. Although an overall analysis on efficacy of CHD for AG could be performed based on these studies, the inadequate taxonomical information limited the further species-level review on some specific herbs.

Conclusions

We recommended that CHD be prescribed as a complementary therapy to WM for atrophic gastritis, but its monotherapy for *H. pylori* eradication is not confirmed by existing clinical evidence. The evidence should be further strengthened because studies at low risk of bias were scarce. More large-scale, multicenter, prospective RCTs are needed therefore. We believe this article will stimulate further evaluation of CHD for AG therapy.

Author contributions

Qing-cai Wang and Ming Zhong act as guarantors for the validity of the study report. Study concept and design: Wen-jie Fang. Acquisition of data: Wen-jie Fang, Xin-ying Zhang and Bo Yang. Checking of data: Xin-ying Zhang and Bo Yang. Analysis and interpretation of data: Xin-ying Zhang. Drafting of the manuscript: Wen-jie Fang. Critical revision of the manuscript: Min Chen, Wan-qing Liao and Wei-hua Pan. Statistical analysis: Wen-jie Fang.

Acknowledgements

We are thankful for the funds provided by 973 Program (2013CB531601 and 2013CB531606), the Severe Infectious Diseases program of the National Health Department (2014ZX09J14106-02A), Institute of Translational Medicine of Changzheng hospital (CZ2016ZH07), the National Natural Science Foundation of China (grant number 81201269, 31270180); Shanghai Science and Technology Committee (grant number 14DZ2272900 and 14495800500).

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